

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
6 January 2005 (06.01.2005)

PCT

(10) International Publication Number  
**WO 2005/001053 A3**

(51) International Patent Classification<sup>7</sup>: **A61K 39/385,**  
39/395

(21) International Application Number:  
PCT/US2004/018451

(22) International Filing Date: 9 June 2004 (09.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/477,796 9 June 2003 (09.06.2003) US

GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant and

(72) Inventor: **WAKSAL, Samuel** [US/US]; 53803-054, FPC Schuylkill, P.O. Box 670, Minersville, PA 17954-0670 (US).

(74) Agents: **SOMERVILLE, Deborah, A. et al.**; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
11 August 2005

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHOD OF INHIBITING RECEPTOR TYROSINE KINASES WITH AN EXTRACELLULAR ANTAGONIST AND AN INTRACELLULAR ANTAGONIST

(57) Abstract: The present invention relates to methods of inhibiting receptor tyrosine kinases by utilizing a combination of both an extracellular and an intracellular RTK antagonist. The extracellular RTK antagonist is a biological molecule or a small molecule that inhibits activation of the receptor tyrosine kinase by interacting with the extracellular binding region of the receptor. The intracellular RTK antagonist is a biological molecule or small molecule that inhibits tyrosine kinase activity of the receptor tyrosine kinase by interacting with the receptor's intracellular region bearing a kinase domain or by interacting with an intracellular protein involved in the signaling pathway of the receptor tyrosine kinase. The present invention also provides methods of treating tyrosine kinase-dependent diseases, and compositions for use in such methods thereof, by administering a combination of both an extracellular and an intracellular RTK antagonist.

WO 2005/001053 A3